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The Alabama Preterm Birth Study: Corticosteroids and neonatal outcomes in 23- to 32-week newborns with various markers of intrauterine infection

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Objective: Intrauterine inflammation/infection is cited as a contraindication to the use of corticosteroids (CS). Our goal was to determine if CS given prenatally to enhance fetal maturity were harmful to infants with various indications of intrauterine infection.

Study design: This was a retrospective analysis of data obtained from 457 consecutively enrolled infants delivered between 23 and 32 weeks. Cultures and a histologic examination of the placenta, and cord blood interleukin (IL)-6 levels were obtained. Neonatal outcomes included periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), chronic lung disease (CLD), necrotizing enterocolitis (NEC), systemic inflammatory response syndrome (SIRS), and infant death.

Results: Of the 457 pregnancies, 57.6% had a positive placental culture, 49.8% had histologic chorioamnionitis/funisitis, 28.8% had elevated cord IL-6 levels, and 12.5% had clinical chorioamnionitis. With intrauterine infection/inflammation, none of the neonatal outcomes were significantly worse if mothers were treated with CS. For those with histologic chorioamnionitis/funisitis, of the outcomes historically improved with CS, RDS (59.9 vs 72.2% $P = .16$), IVH (9.7 vs 14.7% $P = .38$), and neonatal death (9.9 vs 11.1% $P = .82$) all occurred less frequently with CS treatment, but differences were not significant. Similar results were seen for women with a positive placental culture. For women with an elevated IL-6, RDS was significantly reduced (59.4 vs 84.2 %, $P = .045$). Neonatal SIRS was significantly reduced with CS in women with histologic chorioamnionitis/funisitis (39.7 vs 65.7%, $P = .005$), positive placental cultures (32.7 vs 56.3%, $P = .01$), and elevated IL-6 levels (42.7 vs 73.7%, $P = .02$).

Conclusion: In women with intrauterine infection/inflammation, CS use was not associated with significant worsening in any neonatal outcome, and was associated with significant reductions in RDS and SIRS. These data suggest that CS use may not be contraindicated in the presence of intrauterine inflammation/infection.

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Predelivery corticosteroids (CS) to reduce neonatal respiratory distress syndrome (RDS) and enhance fetal maturity is among the best-studied interventions in perinatal medicine.[1-5] In infants born from 24 to 34 weeks gestational age (GA), CS use reduces RDS, intraventricular hemorrhage (IVH), neonatal death, and probably periventricular leukomalacia (PVL) and necrotizing enterocolitis (NEC).[1-5] One concern often raised with CS use is whether they increase the risk of maternal or neonatal infection.[3,4] While the results generally have been reassuring, concern over this issue remains,[2-4] especially in cases where the mother already has clinical evidence of chorioamnionitis.[3] In fact, the 1994 NIH Consensus Panel on The Use of Corticosteroids for Fetal Maturation listed clinical chorioamnionitis as a contraindication to the use of predelivery CS.[3] In this analysis, we evaluated 457 sets of 23- to 32-week mother/newborn dyads, and within those with various markers of intrauterine infection/inflammation, compared the use of CS to a number of newborn outcomes.

Material and methods

This was a retrospective analysis of data from an observational study of 457 consecutive 23- to 32-week liveborn singleton deliveries that occurred between December 5, 1996 and June 13, 2001.[6] A chart review by trained research nurses was performed to gather demographic and obstetric characteristics such as maternal race, history of smoking and preeclampsia, and whether the delivery was spontaneous (following preterm labor or membrane rupture) or indicated (induction or cesarean section before labor for maternal or fetal indications). If the mother received 1 or more doses of CS (always betamethasone) for fetal maturation, this characteristic was considered positive. Gestational age at delivery, infant sex, birth weight, and neonatal outcome data through hospital discharge or death were recorded. Neonatal systemic inflammatory response syndrome (SIRS) was defined as clinically suspected sepsis with negative cerebrospinal fluid and blood cultures or a band: band + polymorphonuclear cell ratio of 0.15 or greater. The diagnoses of grade 3 or 4 IVH or cystic PVL were made using ultrasound criteria.[7] NEC $\geq$ stage 2 was considered present if diagnosed clinically. Respiratory distress syndrome was defined as the documentation of any of 3 criteria: (1) oxygen requirement at 6 through 24 hours of life; (2) an abnormal chest radiograph consistent with RDS within the first 24 hours of life; and (3) need for surfactant. Bronchopulmonary dysplasia (BPD) was defined as infant oxygen requirement at 28 days and chronic lung disease as oxygen requirement at 36 weeks of life. Clinical chorioamnionitis was considered present if diagnosed by the faculty obstetrician, usually for a combination of fever, abdominal pain, and elevated white count.

Placentas for 446 (98%) of the neonates were available and evaluated histologically by a single pathologist (OF-P) using a defined protocol. The free membranes, chorionic plate, and umbilical cord were evaluated for the presence of acute (polymorphonuclear) inflammation.[8-11] With inflammation at any of these sites, the placenta was classified as having histologic chorioamnionitis/funisitis. The chorioamnion interface was cultured for all organisms including *Mycoplasma hominis* and *Ureaplasma urealyticum* as previously described, and were available for 445 women.[12,13] The infant's cord blood was specifically cultured for *Mycoplasma hominis* and *Ureaplasma urealyticum* and results were available for 343 of the infants.[13] A positive culture at any site resulted in classifying the placenta/fetus as culture positive. At delivery, samples of umbilical cord blood were also collected for IL-6 determination and were available for 309 women. Interleukin-6 concentrations were determined by enzyme-linked immunosorbent assay kits (R&D Systems, Inc, Minneapolis, MN). The lower limit of sensitivity of the assay was 0.7 pg/mL. The intra-assay and interassay coefficients of variation were 2.6% and 4.5%, respectively. For this study, values of 34.5 pg/mL, the 95th percentile of women having an indicated birth in this population, were considered elevated. These 164 infants had a mean GA of 28.9 $\pm$ 2.1 weeks, a mean birth weight of 1045 $\pm$ 364 g, and 92% were delivered preterm because of preeclampsia.

Data analyses were performed with SAS version 9 software (SAS Institute, Inc, Cary, NC). Frequencies and means between groups were compared with the use of Chi-square or Fisher exact tests for discrete variables and *t* tests and analysis of variance for continuous variables. Occasionally, data for a specific variable from a specific patient were not available. In these cases, the data for that patient were excluded from both the numerator and denominator when percentages were determined. A P value $\leq$ .05 was chosen to define statistical significance. The study was approved by the UAB Institutional Review Board.

Results

Of the 457 study subjects, 87% received CS and of these, 67% received 2 doses. When the women were divided into those who did (n = 145) and did not have PROM (n = 312), 76% with PROM received CS compared to 92% without PROM. The first column of Table I shows the demographic and obstetric characteristics of the entire study population. About half the mothers were primiparas, 56% were black, 12% smoked, 33% had preeclampsia, and 37% were indicated deliveries. The mean GA was 28.6 $\pm$ 2.1 weeks and the mean birth weight was 1140 $\pm$ 383 g. Columns 3 and 4 show the

Table I The percent of women with various demographic and obstetric factors in the study population (n = 457) and of those women, the percent who did and did not receive corticosteroids

Characteristics	% with characteristic in population	% who received CS	% who did not receive CS	*P* value
Maternal parity (%)				
0	51.4	88.4	11.6	NS
≥1	48.6	85.7	14.2	
Race (%)				
Black	56.1	85.4	14.6	NS
White	41.0	89.3	10.8	
Hispanic	2.0	66.7	33.3	
Other	0.9	100.0	0.0	
Maternal age (y) (%)				
<20	24.9	88.3	11.7	NS
20-30	57.9	85.9	14.1	
>30	17.2	87.2	12.8	
Maternal education (%)				
<12	33.8	85.6	14.4	NS
≥12	66.2	89.1	10.9	
Smoker (%)				
Yes	12.2	85.5	14.6	NS
No	87.8	86.9	13.1	
Diabetes (%)				
Yes	4.8	85.0	15.0	NS
No	95.8	86.2	13.8	
Preeclampsia (%)				
Yes	32.8	95.4	4.6	<.0001
No	67.2	82.3	17.7	
Type of PTB (%)				
Indicated	36.6	95.1	4.9	<.0001
Spontaneous	63.4	81.9	18.1	
Gestational age (%)				
23-24	7.4	85.3	14.7	NS
25-28	42.6	87.3	12.7	
29-32	50.3	86.5	13.5	
BWT (×)	1140 ± 383 g	1134 ± 381 g	1201 ± 452 g	NS
GA (×)	28.6 ± 2.1 wk	28.6 ± 2.2 wk	28.7 ± 3.0 wk	NS

CS, Corticosteroids; *PTB*, preterm birth; *BWT*, birth weight; *GA*, gestational age.

percent of the women with each of these characteristics who did and did not receive CS. Women who had preeclampsia or who had an indicated preterm delivery were more likely to be treated with CS.

In the entire study population, 218/446 (49%) women had histologic chorioamnionitis/funisitis, 252/446 (56%) had a positive placental/cord culture, 81/330 (18%) had an elevated IL-6, and 57/457 (12.5%) had clinical chorioamnionitis. The analysis shown in Table II was performed to determine whether there was an association between CS use and various indicators of placental infection/inflammation. In every case, CS were less likely to be used when the infection/inflammation indicator was present, and in 3 of the 4 cases, the association was significant. Thus, women with markers of placental infection were less likely to have received CS.

Table III shows the newborn outcomes related to various placental markers of infection/inflammation, comparing those who received CS to those who did not. Among those with the various markers of infection/inflammation, none of the neonatal outcomes were significantly worse in those infants treated with CS. For those women with histologic chorioamnionitis/funisitis, of the 3 neonatal outcomes historically improved with CS, RDS (59.9 vs 72.2%, $P = .16$), IVH (9.7 vs 14.7%, $P = .38$), and death (9.9 vs 11.1%, $P = .82$) all occurred less frequently with maternal CS treatment, but the differences were not significant. Similar results were seen for those women with a positive placental culture. Respiratory distress syndrome was significantly reduced (59.4 vs 84.2%, $P = .04$) in women with an elevated cord IL-6 who were treated with CS. Neonatal SIRS was significantly reduced with CS use in women with histologic chorioamnionitis/funisitis (39.7 vs 65.7%, $P = .005$), in those with positive cultures (32.7 vs 56.3%, $P = .01$), and in those with an elevated IL-6

Table II The percent of corticosteroid use when various indicators of placental infection/inflammation were present

Indicators of placental infection	# with indicator	Corticosteroid use (%)		*P* value
		Yes (n = 392)	No (n = 60)	
Histologic chorioamnionitis/funisitis	218	83.5	91.0	.02
Positive placental culture	252	86.1	88.8	NS
IL-6 $\geq$34.5 pg/mL	88	78.4	90.8	.003
Clinical chorioamnionitis	57	70.2	89.1	$<$ .0001

Table III Newborn outcome (%) in infants with various indicators of placental infection/inflammation whose mothers received and did not receive CS

	Histologic chorioamnionitis/ funisitis (n = 218)			Placental culture positive (n = 252)			IL-6 $\geq$34.5 pg/mL (n = 88)			Clinical chorioamnionitis (n = 57)		
Outcome	CS (n = 182)	No CS (n = 36)	*P* value	CS (n = 217)	No CS (n = 35)	*P* value	CS (n = 69)	No CS (n = 19)	*P* value	CS (n = 40)	No CS (n = 17)	*P* value
RDS	59.9	72.2	NS	63.1	76.5	NS	59.4	84.2	.045	60.0	70.6	NS
CLD	7.2	5.6	NS	6.0	11.8	NS	2.9	5.3	NS	7.5	11.8	NS
BPD	18.1	13.9	NS	18.9	23.5	NS	15.9	15.8	NS	25.0	23.5	NS
IVH	9.7	14.7	NS	9.0	15.6	NS	8.7	11.1	NS	10.3	0.0	NS
PVL	4.6	2.9	NS	4.8	3.1	NS	8.7	5.6	NS	10.3	0.0	NS
SIRS	39.7	65.7	.005	32.7	56.3	.01	42.7	73.7	.017	62.5	66.7	NS
NEC	18.7	11.1	NS	16.1	11.8	NS	23.2	15.8	NS	22.5	11.8	NS
Death	9.9	11.1	NS	9.2	14.3	NS	8.7	10.5	NS	7.5	5.9	NS
Sepsis	1.7	0.0	NS	0.9	2.9	NS	1.5	0.0	NS	0.0	5.9	NS

CS, Corticosteroids; *RDS,* respiratory distress syndrome; *CLD,* chronic lung disease; *BPD,* bronchopulmonary displasia; *IVH,* intraventricular hemorrhage; *PVL,* periventricular leukomalacia; *SIRS,* systemic inflammatory response syndrome; *NEC,* necrotizing enterocolitis.

(42.7 vs 73.7, $P = .02$). In the women with clinical chorioamnionitis, there were no significant differences in outcome between those who received and did not receive CS. To further evaluate the risk of CS in women with infection/inflammation, we studied the 41 women with both PROM and clinical chorioamnionitis, 28 who received CS and 13 who did not. There were no significant differences in any outcome between the groups (data not shown). In the entire study population, there were only 6 cases of culture-proven neonatal sepsis. None of these occurred in women with clinical chorioamnionitis treated with CS and there were no significant differences in sepsis rates in any group between those infants whose mothers received and did not receive CS. Of interest is that in each of the groups defined by an indicator of intrauterine infection, the percent of neonates with NEC and PVL was consistently higher in the CS group, although in no case was the difference significant.

In addition, we examined each of the outcomes in the 96 infants who did not have any indication of infection/inflammation. Only 8 of these women did not receive CS. Systemic inflammatory response syndrome was found in 11.5% of those with CS and 12.5% in those without CS, and RDS was found in 72.7% of the infants with CS and 62.5% of the infants without CS.

Comment

There is little doubt that maternal CS treatment between 7 and 1 day before delivery of a $<$34-week preterm newborn improves a number of outcomes including reductions in RDS, IVH, infant death, and probably PVL and NEC.[1-5] The improvements occur regardless of whether the obstetric event leading to delivery was PROM, spontaneous labor, or an indicated delivery secondary to preeclampsia or fetal distress.[5] However, whether CS use is beneficial or harmful in the face of intrauterine infection/inflammation is not clear. When we compared neonatal outcome to CS use within each infection/inflammation group, CS use was not associated with a significant worsening in any neonatal outcome, was associated with significant reductions in RDS and neonatal SIRS, and nonsignificant reductions in IVH and neonatal death. Of some concern was a persistent, but not significant, increase in NEC and PVL. Nevertheless, these data suggest that, overall, the use of CS may not be contraindicated in the face of inflammation/infection, and in fact, may be beneficial.

In a study of infants weighing up to 1750 g, Elimian et al found that in the presence of histologic chorioamnionitis, CS use was associated with significant decreases

in RDS, IVH, PVL, and neonatal death without an increase in neonatal sepsis.[14] This study confirms those results, and extends this observation to cases with positive placental cultures and elevated cord blood IL-6 levels. The results of these 2 studies suggest that CS use in the face of infection/inflammation does not negatively affect most newborn outcomes, and may improve several, especially SIRS and RDS.

Evaluating CS and placental histology from a different viewpoint, Ghidini et al asked the question of whether women who received CS had different placental histologic findings compared to those who did not receive CS.[15] Overall, they found no difference in any histologic parameter. In our study, women who received CS were less likely to have various markers of intrauterine infection/inflammation. While it is impossible to determine cause and effect in nonrandomized observational studies such as these, we would hypothesize that some characteristic(s) of the mothers or their labor and delivery presentation led to decreased CS use in those with infection. We believe it is less likely that CS use changed placental histology.

There are several weaknesses in this paper. First, the diagnosis of clinical chorioamnionitis was based on chart review and did not have predefined criteria for the diagnosis. Also, in this study we did not evaluate the timing of CS use in relationship to the onset of clinical chorioamnionitis or delivery. We assume that CS were not initiated in the presence of clinical chorioamnionitis and the onset of clinical chorioamnionitis occurred after the start of the CS. Another limitation is the absence of a gold standard for an elevated IL-6. We chose the 95th percentile of IL-6 values in the cord bloods of infants who had an indicated preterm birth, but realize this choice was arbitrary. We also understand that because most women received CS, and in most cases fewer than half the women actually had the various markers of inflammation/infection, our power to determine statistically significant differences in outcomes between infants whose mothers received and did not receive CS was often small. Nevertheless, CS used before delivery for fetal maturation in the face of various markers of placental infection/inflammation was not associated with a significant increase in the risk of any adverse neonatal outcome and was associated with an improvement in several.

The nonsignificant increase in NEC and PVL associated with CS use in women with infection/inflammation indicators is cause for concern. However, Elimian et al found a reduction in IVH/PVL with CS use in women with histologic chorioamnionitis and no difference in NEC.[14] Thus, it is likely that the use of CS in women with indicators of intrauterine infection/inflammation has an overall beneficial effect on the neonate. Since clinical chorioamnionitis is associated with a number of adverse neonatal outcomes, we question whether the use of CS should be considered contraindicated in the face of suspected clinical chorioamnionitis, and believe a trial to assess CS use in that situation should be considered.

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